High Incidence of Severe Influenza among Individuals over 50 Years of Age[▽]

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Age-specific epidemiological data on asymptomatic, symptomatic, and severe infections are essential for public health policies on combating influenza. In this study, we incorporated data on microbiologically confirmed infections and seroprevalence to comprehensively describe the epidemiology of pandemic H1N1 2009 influenza. Seroprevalence was determined from 1,795 random serum samples collected in our hospital in January 2007 (before the first wave of the pandemic) and March 2010 (after the second wave). Data on microbiologically confirmed infection and severe cases were obtained from the Centre for Health Protection in Hong Kong. Severe cases were most common in the 51- to 60-year-old age group. The microbiologically confirmed incidence rate was highest for children aged ≤10 years and dropped sharply for the adult population ($\rho = -1.0$; $P < 0.01$), but the incidence rate for severe disease was highest for the 51- to 60-year-old age group. For the 51- to 60-year-old age group, the seroprevalence was similar to that for the younger age groups, but the proportion of severe cases relative to seroprevalence was significantly higher than that for 11- to 50-year-old age groups. As judged from the percentage of specimens positive for other respiratory viruses compared with that for pandemic H1N1 virus, the impact of symptomatic disease due to pandemic H1N1 virus was higher than that for other respiratory viruses in people aged ≤50 years. In conclusion, the 51- to 60-year-old age group, which had the highest overall incidence and the highest rate of severe disease but is currently not considered by the World Health Organization to be an at-risk group, should be prioritized for influenza vaccination in areas where universal influenza vaccination is not practiced.

One of the major criticisms of the handling of pandemic H1N1 2009 influenza by the World Health Organization is the apparent overestimation of its disease severity. Data on age-specific incidence rates from the influenza pandemic can provide a scientific basis for formulating public health policies and insights on the age-related susceptibility to and severity of influenza. Currently, there are discrepancies in the age cutoffs in recommendations for influenza vaccination, especially for adults. While the World Health Organization considers individuals aged ≥65 years to be at a higher risk of severe influenza and includes them as one of the target groups for influenza vaccination and antiviral treatment or prophylaxis (50), the United States Centers for Disease Control and Prevention extended influenza vaccination to all persons aged ≥6 months and, in the event of vaccine shortage, to those aged ≥50 years (18).

To accurately assess the incidence rate and severity of disease, the choice of denominator is crucial (36). If the total number of microbiologically confirmed cases is used as the denominator, this overestimates the severe case incidence rate because infections without microbiological confirmation are excluded. On the other hand, influenza-like illness (ILI) is often used as a surrogate marker for total number of cases, but this may be inaccurate, especially if the surveillance period extends over a long period, when many ILIs may be due to other respiratory pathogens. Other epidemiological studies have used seroprevalence as a measure of the infected population, and these studies have reported a high prevalence in young adults and more severe disease in the pediatric and geriatric populations (27, 30), which may be explained by the immature immune system and immunosenescence, respectively (37, 40). However, most of these studies did not incorporate age-specific data on asymptomatic, symptomatic, and severe infections in their analyses.

In this study, we sought to integrate clinical and laboratory data to evaluate the relative impacts of the H1N1 2009 influenza pandemic on different age groups in the population. The change in seroprevalence provides an estimate of the overall burden of infection (49), whereas the incidence rate of microbiologically confirmed infections represents an estimate of symptomatic cases, as samples were collected mostly from symptomatic patients. The proportion of microbiologically confirmed cases or severe cases in the seropositive population was used to estimate the burden of symptomatic or severe disease in those infected. To assess the relative impact of pandemic H1N1 2009 influenza virus compared to other respi-

ratory viruses, we analyzed the positivity rates for all respiratory specimens tested for respiratory viruses.

MATERIALS AND METHODS

Samples for determination of antibody titers. This study was approved by the institutional review board of the Hospital Authority of Hong Kong. Antibody titers were determined from archived serum samples randomly selected from the Clinical Biochemistry Division, Queen Mary Hospital, in January 2007, before the first wave of the pandemic in the summer of 2009, and in March 2010, after the peak of the second wave. This laboratory provides service to both inpatients and outpatients, with an estimated catchment population of 0.53 million people, or 8% of the Hong Kong population, which should be reasonably representative of the total population of 7 million. Redundant serum samples were excluded by using unique identity card numbers for Hong Kong residents. All samples were coded and remained anonymous during the analysis.

Serological assay. Antibody titers against the pandemic H1N1 2009 influenza virus were determined by hemagglutination inhibition (HI) assay as previously described (7). Briefly, nonspecific inhibitors in serum were removed with a receptor-destroying enzyme (RDE II; Seiken). The treated serum samples were 2-fold serially diluted with phosphate-buffered saline, starting from 1:10. Diluted serum samples were then mixed with 4 hemagglutinin units of pandemic H1N1 2009 influenza virus (A/HK415742/2009) and incubated at room temperature for 1 h. Turkey red blood cells (0.5%) were then added and incubated at room temperature for 30 min before examination for hemagglutination. An HI titer of ≥40 was considered positive.

Microbiologically confirmed influenza cases. Pandemic H1N1 2009 influenza virus infections confirmed microbiologically from 1 May 2009 to 28 February 2010 by the Virology Division, Public Health Laboratory Services Branch, Centre for Health Protection (CHP), Hong Kong, were included in our analysis. This laboratory processes clinical specimens sent for respiratory virus detection from all government hospitals or outpatient clinics spread all over Hong Kong. Respiratory specimens included nasopharyngeal aspirates, nasopharyngeal swabs, throat swabs, tracheal aspirates, and bronchoalveolar lavage fluid. The case definition for microbiologically confirmed cases was a positive reverse transcription-PCR (RT-PCR) test for the pandemic H1N1 2009 influenza virus H1 gene or a positive viral culture from respiratory specimens, as previously reported (32). The decision for microbiological testing was made by the attending clinician. All severe cases during this period were reported to CHP. The case definition for severe pandemic H1N1 2009 influenza requiring notification to CHP included admission to the intensive care unit, a critical condition requiring assisted ventilation or a change of severity from critical to fatal, and microbiological confirmation of pandemic H1N1 2009 influenza virus. The total number of laboratory requests for testing for influenza virus or "other respiratory viruses" was the number of respiratory tract specimens sent to the Virology Division, Public Health Laboratory Services Branch, CHP, Hong Kong, for virus detection. "Other respiratory viruses" included seasonal influenza A (H1N1) virus, influenza A (H3N2) virus, influenza B virus, adenovirus, parainfluenza virus, respiratory syncytial virus, and rhinovirus.

Definitions. The seroprevalence (%) was obtained by dividing the number of serum samples with HI titers of ≥40 by the total number of nonredundant sera tested. The infected population in each age group was estimated by the percent change in seroprevalence between 2007 and 2010 multiplied by the population number (34). The incidence rate of symptomatic disease was obtained by dividing the number of microbiologically confirmed cases by the population of the age group, whereas the incidence rate of severe disease was obtained by dividing the number of notified severe disease cases by the population of the age group. The burden of symptomatic or severe disease was estimated by the proportion of incidence in the infected population.

Statistical analysis. The relationship between age and incidence rate was assessed by Spearman correlation. The chi-square test for trends was used to assess the proportions of positive specimens for pandemic H1N1 2009 influenza virus and other respiratory viruses in different age groups. The risk ratios of influenza for the 51- to 60-year-old age group and the younger age groups were calculated. The statistical analysis was performed using SPSS software, version 18.0 for Windows (SPSS), R statistical environment, version 11.1, or VassarStats (http://faculty.vassar.edu/lowry/VassarStats.html).

RESULTS

Seroprevalence was estimated by HI testing of 1,795 serum samples, of which 795 and 1,000 samples were collected in 2007

TABLE 1. Number of serum samples collected for each age group[a]

Age group (yr)	No. of serum samples collected in 2007
0–10	13
11–20	74
21–30	81
31–40	81
41–50	81
51–60	72
61–70	81
71–80	95
81–90	96
≥91	121

[a] The number of serum samples collected in 2010 was 100 for each age group.

and 2010, respectively (Table 1). In 2007, the seropositive rate was 8.8%. Preexisting cross-reactive antibodies against pandemic H1N1 2009 influenza virus were found mainly in patients aged ≥71 years and were more prevalent in the older age groups (Fig. 1). Cross-reactive antibodies were also found in 2.1% of individuals aged 21 to 50 years. No children of ≤10 years of age or adults between 51 and 70 years old were seropositive in 2007. In 2010, the overall seropositive rate was 22.9%. Differences in HI titers between baseline and 2010 were not statistically significant for adults of 71 years of age and older. Therefore, we could not use seroprevalence to accurately predict the overall incidence rate of infection in the population of ≥71-year-olds.

Between 1 May 2009 and 28 February 2010, a total of 27,116 microbiologically confirmed cases of pandemic H1N1 2009 influenza virus infection were found. Of the 255 severe cases reported, 157 were in males and 98 were in females, with a median age of 51 years. The 51- to 60-year-old age group had the largest number of severe cases, accounting for 29.4% of the total number of severe cases (Fig. 2). The incidence rate of microbiologically confirmed pandemic H1N1 2009 influenza was highest for the ≤10-year-old age group and dropped sharply with increasing age (ρ = −1.0; P < 0.01), while the incidence rate of severe cases showed an apparent bimodal distribution, with higher incidence rates for the age group of ≤10-year-olds and for those older than 50 years (Fig. 3). The highest incidence rate of severe disease also occurred in the 51- to 60-year-old age group, with a significantly higher risk than those for other, younger age groups (Table 2).

The proportion of microbiologically confirmed cases or severe disease cases relative to the infected population number was used to estimate the burden of symptomatic or severe disease in the infected population for different age groups (Fig. 4). While the burden of symptomatic disease was highest in the ≤10-year-old age group, severe disease occurred most frequently in the older population, starting to rise in the 51- to 60-year-old age group (Fig. 4 and Table 2).

We also assessed the impact of pandemic H1N1 2009 influenza virus infection relative to that of other respiratory viral infections in different age groups by analyzing the positivity rates of respiratory tract specimens. The pandemic H1N1 2009 influenza virus was detected more frequently than other respiratory viruses in age groups with persons of ≤60 years of age, but other respiratory viruses predominated in age groups with
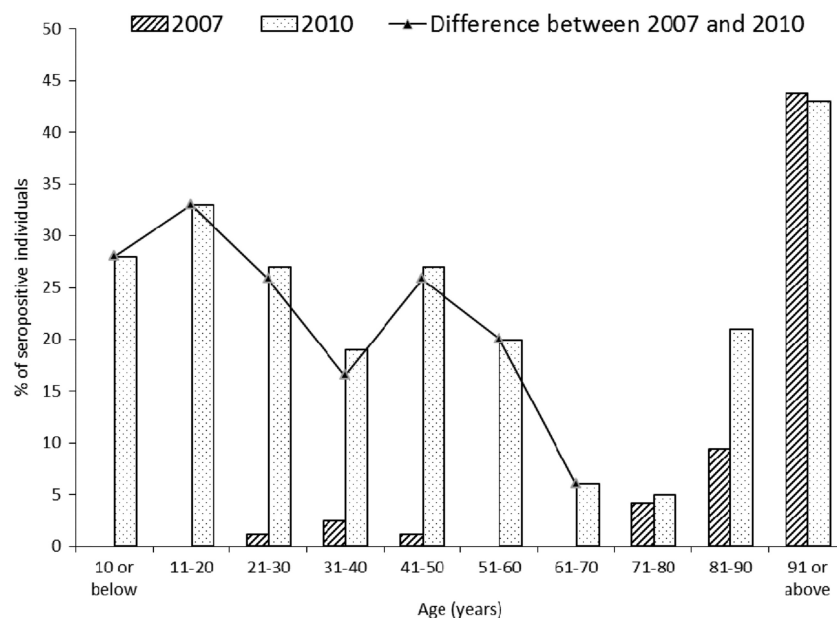
FIG. 1. Proportions of seropositive individuals in 2007 and 2010. The *y* axis represents the percentage of seropositive individuals detected (those with hemagglutination inhibition antibody titers of ≥40).

persons of >60 years of age (Fig. 5). The percentage of specimens positive for pandemic H1N1 2009 influenza virus decreased with increasing age (chi-square test for trend χ^2 value = 13,380.73; $P < 0.001$). Though a significant trend was still observed for other respiratory viruses, its magnitude was much less than that for pandemic H1N1 2009 influenza virus (chi-square test for trend χ^2 value = 366.969; $P < 0.001$). It should be noted that the percentages of specimens positive for other respiratory viruses were not significantly different ($P > 0.05$) between 51- to 60-year-olds and 41- to 50-year-olds, suggesting
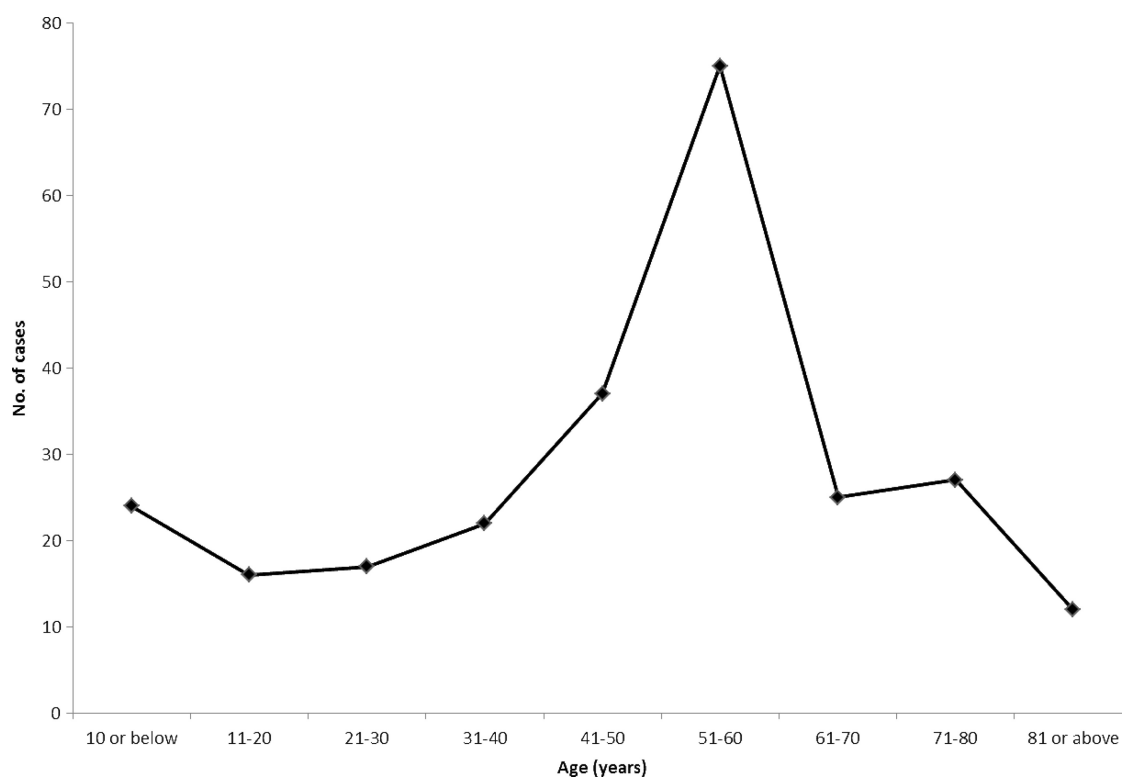

FIG. 2. Incidence of severe cases of pandemic H1N1 2009 influenza virus infection. The *y* axis represents the absolute number of severe cases, defined by admission to the intensive care unit, a critical condition requiring assisted ventilation, or a change of severity from critical to fatal.
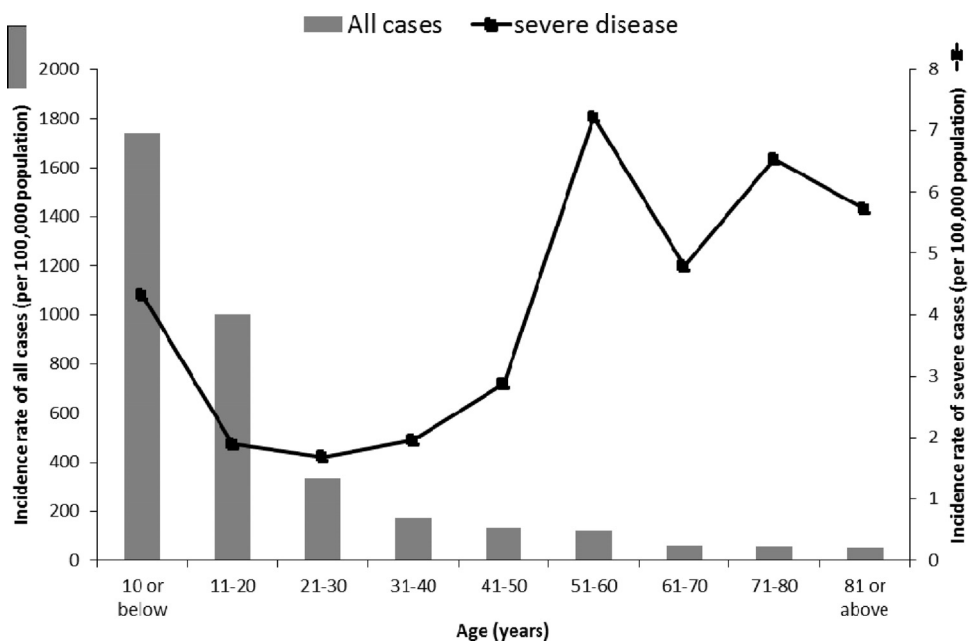
FIG. 3. Microbiologically confirmed incidence rates of pandemic H1N1 2009 influenza (per 100,000 population members). The *y* axis on the left represents the incidence rate of all cases with a positive virological test for pandemic H1N1 2009 influenza virus, while the *y* axis on the right shows the incidence rate of all severe cases.

that there was no sampling bias in terms of specimen collection in these age groups.

DISCUSSION

In this study, we systematically analyzed and compared the age-specific incidence rates of pandemic H1N1 2009 influenza by using serial serological data and data on microbiologically confirmed infections encompassing all age groups. The pandemic H1N1 2009 influenza virus affected children and adolescents more frequently than older adults, as evidenced by the greater difference between prepandemic and postpandemic seroprevalences, the higher age-specific incidence rate of microbiologically confirmed infection, and the higher positivity rate in respiratory tract specimens than that for other respiratory viruses. The 51- to 60-year-old age group accounted for the largest number of severe cases, and this age group also had the highest incidence rate of severe cases. By analyzing the positivity rate in respiratory tract specimens, we have also shown that the pandemic H1N1 2009 influenza virus was the predominant respiratory virus affecting the population aged 50 years or less.

TABLE 2. Risk ratios of severe disease between 51- to 60-year-old age group and younger age groups

Age group (yr)	Risk ratio (incidence rate)	95% confidence interval	Risk ratio (burden)	95% confidence interval
10 or below	1.164	1.041–1.301	1.326	1.186–1.483
11–20	1.496	1.361–1.645	1.933	1.758–2.126
21–30	1.608	1.458–1.772	1.838	1.667–2.025
31–40	1.610	1.446–1.794	1.464	1.314–1.631
41–50	1.500	1.317–1.710	1.741	1.528–1.983

The main advantage of using the difference in prepandemic and postpandemic seroprevalences to estimate the incidence rate is that even asymptomatic cases are captured. Numerous seroprevalence studies of pandemic H1N1 2009 influenza have been published (1–4, 8, 9, 11, 15, 16, 19, 20, 29, 31–35, 39, 41, 43, 44, 46, 51–54), but unlike our study, many of them did not incorporate the incidence rate of microbiologically confirmed cases or severe cases. Other studies which have compared seroprevalences with microbiologically confirmed data either did not include all age groups (51) or did not perform age-specific analysis (33).

The World Health Organization includes adults of 65 years of age or older as a risk group for severe disease and as one of the target groups for influenza vaccination and antiviral treatment or prophylaxis (50). This is supported by our finding that the burden of severe disease is highest in the 61- to 70-year-old age group and is consistent with other studies which have shown that those aged ≥60 or ≥65 years have higher case-fatality ratios (10, 14, 17). However, we have also demonstrated that the 51- to 60-year-old age group has the highest incidence rate of severe disease among all age groups and a higher burden of severe disease than that for younger age groups. Our result is comparable to worldwide estimates obtained by using laboratory-confirmed cases as the denominator in the calculation for the rate of severe cases, as the 50- to 64-year-old age group had the highest relative risk of admission to an intensive care unit for most countries (47). Likewise, a study from California showed that the highest incidence rate of death occurred in those aged 50 to 59 years (30). However, neither study estimated the burden of severe disease in all infected individuals by monitoring the change in seroprevalence before and after the first wave. Rather, they used the total population as the denominator for the analysis. The find-
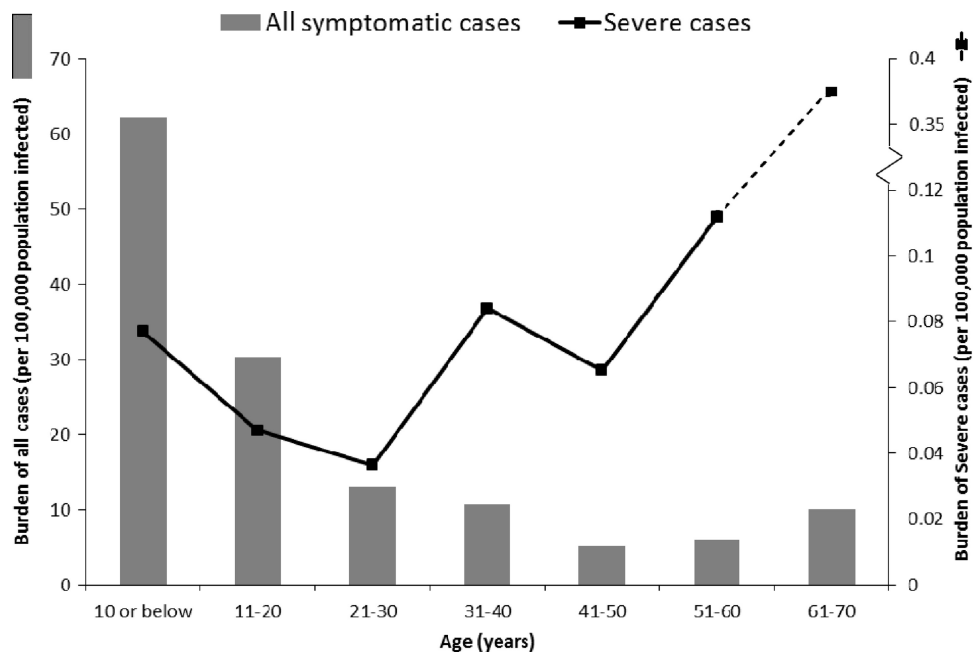
FIG. 4. Burden of symptomatic or severe disease. The infected population was estimated by seroprevalence. The *y* axis on the left represents the burden for all cases, while the *y* axis on the right shows the burden for severe cases.

ings of these two studies and our study are consistent with the recommendations of the United States Centers for Disease Control and Prevention in that individuals aged ≥50 years should have priority for vaccination in the event of vaccine shortage (18). Our finding was unlikely to be caused by specimen collection bias, as the positivity rate for other respiratory viruses was not different from that for the 41- to 50-year-old age group. The high incidence rate of severe disease in this age

group therefore justifies lowering the age cutoff for the high-risk group from 65 to 51 years old.

The burden of symptomatic disease was lowest in the age groups including persons aged 21 to 60 years, suggesting that there were many patients with mild disease who did not require medical attention and therefore were not tested for respiratory viruses in this age group. This result is consistent with the findings of another large prospective study in which most pa-
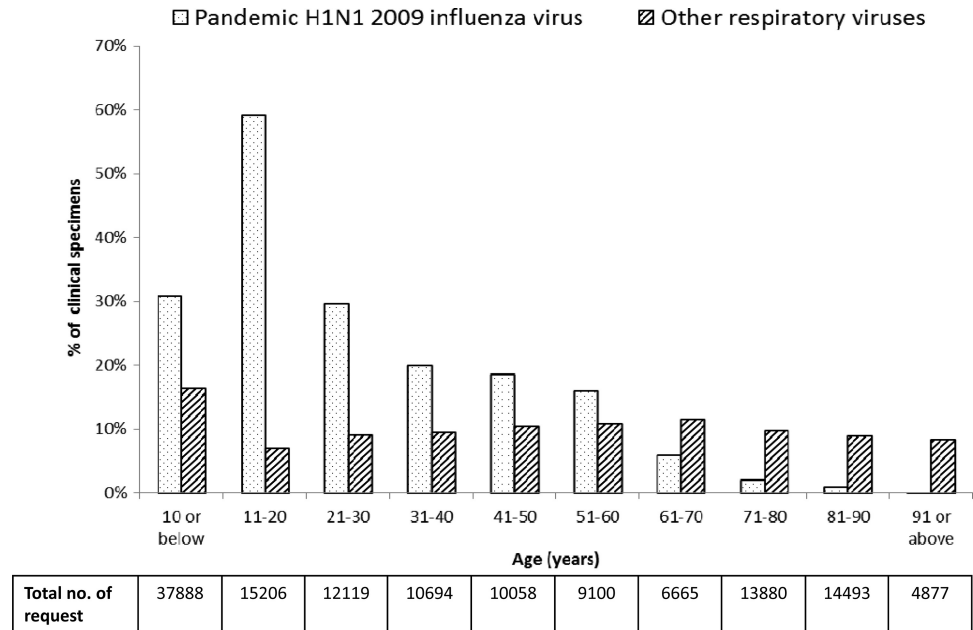

	10 or below	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91 or above
Total no. of request	37888	15206	12119	10694	10058	9100	6665	13880	14493	4877

FIG. 5. Proportions of clinical specimens positive for pandemic H1N1 2009 influenza virus and other respiratory viruses. The *y* axis represents the percentage of clinical specimens that tested positive for influenza virus or other respiratory viruses.

tients in this age group were only mildly symptomatic (6). The burden of severe disease was also lower in the age groups including persons aged 21 to 60 years than in older age groups. Despite such a low burden of severe disease, the absolute numbers of severe cases in these age groups were actually higher than in those above 60 years old, similar to the case in previous studies (13, 25, 28, 38, 45, 48), because a large proportion of the population in these age groups was infected due to the lack of preexisting cross-reactive antibodies against the pandemic H1N1 influenza virus. We also speculate that this particular age group has developed a solid cell-mediated immunity due to a cytotoxic T lymphocyte response or nonneutralizing antibody-dependent cellular cytotoxicity against the highly conserved viral antigens on the viral matrix or nucleoprotein (12, 26), which is important in recovery from the illness. Such relative protection induced by repeated exposure before and after the age of 20 years decayed with age-associated immunosenescence or was impaired by major underlying disease in those over 50 years of age.

The overall postpandemic seroprevalence of 22% in our study is in the lower range of estimates from previous seroprevalence studies, which have shown estimated infection rates of 5 to 60% (5). The wide range of estimates may be accounted for by differences in the ethnic groups of the studied populations, the serological assay used (HI versus viral neutralization assays), and the timing of specimen collection (after the first or second wave). In our study, we also noted a bimodal distribution of prepandemic seroprevalences, with cross-reactive antibodies (HI titer of ≥40) found in a small number of individuals aged 21 to 50 years and in more of those aged over 70 years. This finding is consistent with other studies in which the seropositive rate was slightly higher in those born in the 1970s and 1980s (2, 19, 22, 32). However, this observation was not seen in other studies (24, 33). The reason for the low level of cross-reactive antibodies is not known.

There are several limitations of this study. Factors associated with lower rates of seroconversion have been described, including older age, being female, being pregnant, or having milder disease (7, 9, 32, 42). Notably, 10% of convalescent-phase plasma donors of influenza virus had HI titers of <40 (21). These factors contribute to a lower seroprevalence rate, which leads to an underestimation of the incidence of infection. In contrast, vaccination leads to seroconversion, and therefore seroprevalence may overestimate the incidence of infection in areas where vaccine coverage is high. However, the pandemic H1N1 vaccination uptake rate was very low in Hong Kong after one widely publicized report of a suspected influenza-related complication of Guillain-Barre syndrome in a medical doctor. Up to 31 March 2010, only 188,622 individuals in the Hong Kong influenza vaccination program (2.7% of the total Hong Kong population) had received the monovalent pandemic H1N1 vaccine, while an additional 61,107 doses of vaccine had been distributed to private practitioners for individuals who were excluded from the at-risk target group in the vaccination program. However, the exact number of vaccinees in the private sector outside the government vaccination program is not known, as these data are not reported to the CHP. But even if this batch of vaccine were all administered to patients, the percentage of vaccinated population would be only 3.6%. Therefore, the effect of vaccination is negligible.

Furthermore, the number of available prepandemic serum samples for the ≤10-year-old age group was low, so we may not have been able to detect individuals who were seropositive. However, since other studies of this age group showed very low prevalence rates of preexisting antibody of <5% (34), the interpretation of our results should be similar for this age group. Unexpectedly, there were unexplained small changes in seropositivity between 2007 and 2010 for the 61- to 80-year-old age groups. Finally, the differences in rates of severe infection may have been confounded by factors such as underlying diseases. In our study, we found a higher incidence of severe infection in the 51- to 60-year-old age group. In Hong Kong, 22.5% of the population in the age group of 50- to 59-year-olds has chronic diseases, compared to 2.8 to 10.7% of those aged less than 50 years (23). We were not able to access the clinical data for each patient, as the serum samples were coded anonymously. Further studies incorporating underlying diseases will allow an assessment of the independent effect of age on severity in this age group.

While adolescents and younger adults were most commonly affected by the pandemic H1N1 2009 influenza virus, the clinical consequences were most alarming for older adults. In contrast to the usual age cutoff of 65 years, our results clearly demonstrate that individuals of more than 50 years of age are more prone to severe infection than the younger population. In view of our findings, health authorities should consider lowering the at-risk group from those above 65 years of age to those above 51 years of age.

ACKNOWLEDGMENTS

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